Initiating Antiretroviral Therapy in Treatment-Naive Patients (Updated January 10, 2011)

Panel's Recommendations:

- ***Antiretroviral therapy (ART) should be initiated in all patients with a history of an AIDS-defining illness or with a CD4 count <350 cells/mm^3 (AI).***
- ***ART is also recommended for patients with CD4 counts between 350 and 500 cells/mm^3 (A/B*-II).***
- ***ART should be initiated, regardless of CD4 count, in patients with the following conditions: HIV-associated nephropathy (HIVAN) (AII) and hepatitis B virus (HBV) coinfection when treatment of HBV is indicated (AIII).***
- ***A combination antiretroviral (ARV) drug regimen is also recommended for pregnant women who do not meet criteria for treatment with the goal to prevent perinatal transmission (AI).***
- ***For patients with CD4 counts >500 cells/mm^3, Panel members are evenly divided: 50% favor starting ART at this stage of HIV disease (B); 50% view initiating therapy at this stage as optional (C) (B/C-III).***
- ***Patients initiating ART should be willing and able to commit to lifelong treatment and should understand the benefits and risks of therapy and the importance of adherence (AIII). Patients may choose to postpone therapy, and providers, on a case-by-case basis, may elect to defer therapy based on clinical and/or psychosocial factors.***

Rating of Recommendations: A = Strong; B = Moderate; C = Optional
Rating of Evidence: I = data from randomized controlled trials; II = data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = expert opinion

* ***Panel members are divided on the strength of this recommendation: 55% voted for strong recommendation (A) and 45% voted for moderate recommendation (B).***

The primary goal of ART is to reduce HIV-associated morbidity and mortality. This is best accomplished by using ART to maximally inhibit HIV replication, as measured by consistent plasma HIV RNA (viral load) values below the level of detection using commercially available assays. Additional benefits of ART, supported by accumulating evidence, are reduction in HIV-associated inflammation and its associated complications and reduction in HIV transmission.

Over the past 20 years, the Panel has made several changes to the recommendations on when to start therapy based on prevailing clinical trial and cohort data and therapeutic options available at the time of each revision. The standard procedure for the Panel is to only make recommendations in agreement with two-thirds of the Panel members. This has not been possible for the ***When to Start*** recommendations in this version of the guidelines. Accordingly, the breakdown of votes is presented for recommendations supported by less than two-thirds of Panel members.

Randomized controlled trials provide evidence supporting the benefit of ART in patients with CD4 counts $\leq$350 cells/mm^3. However, such evidence showing benefit for patients with higher CD4 cell counts is not yet available. Based on cumulative observational cohort data demonstrating benefits of ART in reducing AIDS- and non-AIDS-associated morbidity and mortality, the Panel now recommends ART for patients with CD4 count between 350 and 500 cells/mm^3 **(A-B/II)**. For patients with CD4 count >500 cells/mm^3, Panel members are evenly divided: 50% favor starting ART at earlier stages of HIV disease **(BIII)**; 50% view initiating therapy at this stage as optional **(CIII)**.

Panel members favoring earlier initiation of therapy base their recommendation on several recent developments: (1) report from at least one recent cohort study demonstrating survival benefit with initiation of ART at CD4 count >500 cells/mm^3; (2) growing awareness that untreated HIV infection may be associated with development of many non-AIDS-defining diseases, including cardiovascular disease, kidney disease, liver disease, and malignancy; (3) availability of ARV regimens that are more effective, more convenient, and better tolerated than ARV combinations no longer in use; and (4) increasing evidence that effective ART reduces HIV transmission **(BIII)**.

The other 50% of the Panel members feel that current evidence does not definitively demonstrate clear benefit of ART in all patients with CD4 count >500 cells/mm^3. They also feel that risks of short- or long-term drug-related complications, nonadherence to lifelong therapy in asymptomatic patients, and potential for development of drug

resistance may offset possible benefits of earlier initiation of therapy. Thus, pending more definitive supporting evidence, these Panel members recommend that therapy in this setting should be optional and considered on a case-by-case basis **(CIII)**.

The known benefits, risks, and limitations of ART, as well as the strength of the recommendations according to CD4 count levels, are discussed below.

BENEFITS OF ANTIRETROVIRAL THERAPY

Earlier studies definitively showed that potent combination ART improves survival and reduces AIDS-related complications in patients with advanced HIV disease. There is now increasing evidence demonstrating the benefits of viral suppression and immunologic responses on reducing mortality and non-AIDS-related complications in patients with higher pretreatment CD4 counts. The following is a focused discussion of the rationale that forms the basis for the Panel's recommendation favoring earlier treatment.

Reduction in Mortality and/or AIDS-Related Morbidity

Patients with a history of an AIDS-defining illness or CD4 count <350 cells/mm^3

HIV-infected patients with CD4 counts <200 cells/mm^3 are at higher risk of opportunistic diseases, non-AIDS morbidity, and death. Randomized controlled trials in patients with CD4 counts <200 cells/mm^3 and/or a history of an AIDS-defining condition provide strong evidence that ART improves survival and delays disease progression in these patients *[1-3]*. Long-term data from multiple observational cohort studies evaluating earlier ART (>200 cells/mm^3) compared with later treatment (<200 cells/mm^3) have also provided strong support for these findings *[4-8]*.

Few large, randomized controlled trials address when to start therapy in patients with CD4 counts >200 cells/mm^3. CIPRA HT-001 is a randomized clinical trial conducted in Haiti. Study participants were randomized to start ART at CD4 counts of 200–350 cells/mm^3 or to defer treatment until their CD4 counts dropped below 200 cells/mm^3 or they developed an AIDS-defining condition. In an interim analysis of the study, a higher mortality rate (hazard ratio [HR] = 4.0, p = 0.0011) and greater incident tuberculosis (HR = 2.0, p = 0.0125) were observed among patients who deferred therapy compared with participants who began ART with CD4 counts of 200–350 cells/mm^3 *[9]*. This evidence led to the study Data Safety Monitoring Board's recommendation to terminate the trial before completion.

The SMART study was a multinational trial enrolling more than 5,400 participants with CD4 counts >350 cells/mm^3. Participants were randomized to continuous ART or to treatment interruption until CD4 count dropped to <250 cells/mm^3. In a subgroup analysis involving the 249 study participants who were ART naïve at enrollment, a trend of lower risk of serious AIDS- and non-AIDS-related events was seen in those who initiated therapy immediately compared with those who deferred therapy until CD4 count dropped to <250 cells/mm^3 (p = 0.06) *[10]*.

Collectively, these studies support the Panel's recommendation that ART should be initiated in patients with a history of an AIDS-defining illness or with a CD4 count <350 cells/mm^3 **(AI)**.

Patients with a CD4 count between 350 and 500 cells/mm^3

There are no randomized trials using current combination regimens in patients with CD4 counts >350 cells/mm^3 to provide data that directly address the question of when to start therapy in patients with CD4 counts of 350–500 cells/mm^3. Data from the ART Cohort Collaboration (ART-CC), which included 61,798 patient-years of follow-up, showed a declining risk of AIDS or death for up to 5 years in subjects starting therapy with a CD4 count ≥350 cells/mm^3 compared with subjects starting between 200 and 349 cells/mm^3 *[11]*. A more recent rigorous analysis of this cohort found that deferring therapy until the 251 to 350 cells/mm^3 range was associated with a higher rate of progression to AIDS and death compared with initiating therapy in the 351 to 450 cells/mm^3 range (risk ratio: 1.28, 95% confidence interval [CI]: 1.04 to 1.57) *[6]*.

In a collaboration of North American cohort studies (NA-ACCORD) that evaluated patients regardless of whether they had started therapy, the 6,278 patients who deferred therapy until CD4 counts were <350 cells/mm^3 had an increased risk of death compared with 2,084 patients who initiated therapy with CD4 counts between 351 and 500 cells/mm^3 (risk ratio: 1.69, 95% CI: 1.26 to 2.26) after adjustment for other factors that differed between these two groups *[12]*.

When interpreting both of these cohort studies it is important to note that although the relative risk of a mortality event is evident, the overall number of events was small. In these cohort studies, the relative risks determined could have been influenced by unmeasured confounders that cannot be adjusted for in the analysis. The findings from these observational cohort studies point to potential harm if therapy is deferred until CD4 count falls to <350 cells/mm^3. Based on these findings, combined with emerging biologic evidence regarding potential damage to end organs from inflammation associated with untreated HIV replication and the potential reduction in HIV transmission with treatment (see below), the Panel recommends initiation of ART in patients with CD4 counts between 350 and 500 cells/mm^3. Panel members are divided on the strength of this recommendation: 55% voted for strong recommendation (A) and 45% voted for moderate recommendation (B) **(A/B-II)**.

Patients with a CD4 count >500 cells/mm^3

The NA-ACCORD study also observed patients who started treatment at CD4 counts >500 cells/mm^3 or after CD4 counts dropped below this threshold. The adjusted mortality rates were significantly higher among the 6,935 patients who deferred therapy until CD4 count fell to <500 cells/mm^3 compared with rates in the 2,200 patients who started therapy while CD4 count was > 500 cells/mm^3 (risk ratio: 1.94, 95% CI: 1.37 to 2.79) *[12]*. Although large and generally representative of care in the United States, the study has several limitations, including the small number of deaths and the potential for unmeasured confounders that might have influenced outcomes independent of ART.

In contrast, analysis of the ART-CC cohort failed to identify a benefit for patients initiating ART with CD4 counts > 450 cells/mm^3. This analysis also did not identify a harmful effect of this strategy *[6]*. Deferral of therapy to the 351–450 cells/mm^3 range was associated with a similar rate of progression to AIDS/death compared with initiation of therapy in the 451–550 cells/mm^3 range (risk ratio: 0.99, 95% CI: 0.76 to 1.29). This study also found that the proportion of patients with CD4 counts between 451 and 550 cells/mm^3 who would progress to AIDS or death before having a CD4 count <450 cells/mm^3 was low (1.6%; 95% CI: 1.1 to 2.1%).

Based on these data, along with a better understanding of the pathogenesis of HIV infection and the growing awareness that untreated HIV infection increases the risk of many non-AIDS-defining diseases (see below), 50% of Panel members favor initiation of ART in HIV-infected persons with a CD4 count >500 cells/mm^3 **(BIII)**.

The other 50% of the Panel members are reluctant to broadly recommend starting ART at higher CD4 cell counts and consider that therapy should be optional at this stage of HIV disease **(CIII)**. In making this recommendation, the Panel members note that the amount of data supporting initiation of therapy decreases as the CD4 count increases above 350–500 cells/mm^3, and that concerns remain over the unknown overall benefit and long-term risks with earlier treatment.

When discussing starting ART at higher CD4 cell counts (>500 cells/mm^3), clinicians should inform patients that data on the clinical benefit of starting treatment at such levels is not conclusive. There is a need for further ongoing research (both with randomized clinical trials and cohort studies) to assess the short- and long-term clinical and public health benefits and cost effectiveness of starting therapy at higher CD4 counts. Such research findings will provide guidance for future recommendations by the Panel.

Effects of Antiretroviral Therapy on HIV-Related Morbidity

HIV-related morbidity and mortality derive not only from immune deficiency but also from direct effects of HIV on specific end organs and the indirect effects of HIV-associated inflammation on these organs. In general, the available data demonstrate that:

- Untreated HIV infection may have detrimental effects at all stages of infection.
- Treatment is beneficial even when initiated later in infection. However, later therapy may not repair damage associated with viral replication during early stages of infection.

- Earlier treatment may prevent the damage associated with HIV replication during early stages of infection.

Clinical studies have demonstrated that sustaining viral suppression and maintaining higher CD4 count, mostly as a result of effective combination ART, delay or prevent some non-AIDS-defining complications, such as HIV-associated kidney disease. Sustained viral suppression and immune recovery may also delay or prevent other disorders, such as liver disease, cardiovascular disease, and malignancies, as discussed below.

HIV-associated nephropathy (HIVAN)

HIVAN is the most common cause of chronic kidney disease in HIV-infected individuals that may lead to end-stage kidney disease *[13]*. HIVAN is seen almost exclusively in black patients and can occur at any CD4 count. Ongoing viral replication appears to be directly involved in renal injury *[14]*. HIVAN is extremely uncommon in virologically suppressed patients *[15]*. ART in patients with HIVAN has been associated with both preserved renal function and prolonged survival *[16-18]* and therefore should be started in these patients **(AII)**.

Coinfection with hepatitis B virus (HBV) and/or hepatitis C virus (HCV)

HIV infection is associated with more rapid progression of viral hepatitis-related liver disease, including cirrhosis, end-stage liver disease, hepatocellular carcinoma, and fatal hepatic failure *[19-20]*. Although the mechanisms of accelerated liver disease in HIV-infected patients have not been fully elucidated, HIV-related immunodeficiency and a direct interaction of HIV with hepatic stellate and Kupffer cells have been implicated *[21-24]*. ART may attenuate liver disease progression in persons coinfected with HBV and/or HCV by preserving or restoring immune function and reducing HIV-related immune activation and inflammation *[25-27]*. ARV drugs active against both HIV and HBV (e.g., tenofovir disoproxil fumarate [TDF], lamivudine [3TC], emtricitabine [FTC]) may also prevent the development of significant liver disease by directly suppressing HBV replication *[28-29]*. Although ARV drugs do not directly inhibit HCV replication, HCV treatment outcomes may be improved if HIV replication is controlled or if CD4 counts are increased *[30]*. The presence of chronic viral hepatitis increases the risk of ARV-induced liver injury; however, the majority of coinfected persons do not develop clinically significant liver injury, particularly those receiving recommended ARV regimens *[31-33]*. Some studies suggest that the rate of hepatotoxicity is greater in persons with more advanced HIV disease. Nevirapine (NVP) toxicity is a notable exception: the hypersensitivity reaction and associated hepatotoxicity to this drug are more frequent in patients with higher CD4 cell counts *[34]*. Collectively, these data suggest earlier treatment of HIV infection in persons coinfected with HBV, and possibly HCV **(CIII)**, may reduce the risk of liver disease progression. Furthermore, ART including drugs active against both HIV and HBV should be started in all patients coinfected with HBV who are also going to receive HBV treatment **(AIII)**.

Cardiovascular disease

Cardiovascular disease is a major cause of mortality among HIV-infected patients, accounting for a third of serious non-AIDS conditions and at least 10% of deaths among HIV-infected patients *[35-36]*. Studies link exposure to specific ARV drugs to a higher risk of cardiovascular disease *[37-38]*. Certain HIV treatment regimens are associated with a more atherogenic lipid profile as assessed by lipoprotein particle size analysis among HIV-infected men compared with uninfected controls *[39]*. Untreated HIV infection may also be associated with an increased risk of cardiovascular disease. In some cross-sectional studies, patients with HIV have higher levels of markers of inflammation and endothelial dysfunction than HIV-uninfected controls *[40-42]*. In two randomized trials, markers of inflammation and coagulation increased following treatment interruption *[43-44]*. One study suggests that ART may improve endothelial function *[45]*.

In the SMART study, the risk of cardiovascular events was greater in participants randomized to CD4-guided treatment interruption compared with participants who received continuous ART *[46]*. In other studies, ART resulted in marked improvement in parameters associated with cardiovascular diseases, including markers of inflammation (e.g., interleukin 6 [IL-6] and high sensitivity C-reactive protein [hsCRP]) and endothelial dysfunction *[41, 45]*. There is also a modest association between lower CD4 count while on therapy and short-term risk of cardiovascular disease *[42, 47-48]*. However, in at least one of these cohorts (the CASCADE study), the link between CD4 count and fatal cardiovascular events was no longer statistically significant when adjusting for plasma HIV RNA level. Collectively, the data linking viremia and endothelial dysfunction and inflammation, the increased risk of cardiovascular events

with treatment interruption, and the association between cardiovascular disease and CD4 cell depletion suggest that early control of HIV replication with ART can be used as a strategy to reduce cardiovascular disease risk **(BIII)**.

Malignancies

Several population-based analyses suggest increased incidence of non-AIDS-associated malignancies during chronic HIV infection. The incidence of non-AIDS malignancy in HIV-infected subjects is higher than in matched HIV-uninfected controls *[49]*. Large cohort studies of mostly patients receiving ART have reported a consistent link between low CD4 counts (<350–500 cells/mm^3) and the risk of AIDS- and/or non-AIDS-defining malignancy *[42, 47, 50-53]*. The ANRS C04 Study demonstrated a statistically significant relative risk of all cancers evaluated (except for anal carcinoma) in patients with CD4 counts <500 cells/mm^3 compared with patients with current CD4 counts >500 cells/mm^3 and a protective effect of ART for HIV-associated malignancies *[50]*. This potential effect of HIV-associated immunodeficiency is particularly striking with regard to cancers associated with chronic viral infections (e.g., HBV, HCV, human papilloma virus [HPV], Epstein-Barr virus [EBV], human herpes virus-8 [HHV-8]) *[54-55]*. Cumulative HIV viremia itself may also be associated with the risk of non-Hodgkin lymphoma and other AIDS-defining malignancies, independent of other factors *[53, 56]*. Together this evidence suggests that initiating ART to suppress HIV replication and maintain CD4 counts at above 350–500 cells/mm^3 may reduce the risk of both AIDS-defining and non-AIDS-defining malignancies **(CIII)**.

Neurocognitive decline

Early in the HIV epidemic, HIV was identified in brain tissue *[57]* and assumed to be the cause of AIDS dementia complex *[58]*. The improvement of AIDS dementia complex symptoms with the use of ART supported this assumption *[59-60]*. The CASCADE observational cohort reported a dramatic decline in the incidence of HIV-associated dementia from 6.49 per 1,000 person-years (before 1997) to 0.66 per 1,000 person-years (2003–2006), after the widespread use of potent ART *[61]*. In this cohort, having a current CD4 count >350 cells/mm^3 was associated with the lowest risk of developing HIV-associated dementia. HIV infection has also been associated with a number of less severe neurologic complications, including changes in neuropsychological ability, speed of processing, and everyday functioning *[62]*. Such syndromes also were predicted by a lower pretherapy CD4 nadir and/or by CD4 count while on therapy *[63-64]*. Additional clinical data are needed to determine the relative roles of ongoing HIV replication and potential neurotoxicity of ARV agents in the development of neurocognitive dysfunction. Whether early initiation of therapy will prevent HIV-associated neurocognitive dysfunction remains unclear. However, the neurological complications that may accompany uncontrolled HIV replication and CD4 depletion suggest a potential benefit of earlier initiation of ART **(CIII)**.

Age and treatment-related immune reconstitution

The CD4 cell response to ART is an important predictor of short-term and long-term morbidity and mortality. Treatment initiation at an older age is consistently associated with a less robust CD4 count response; starting therapy at a younger age may result in better immunologic and perhaps clinical outcomes *[65-67]***(CIII)**.

T-cell activation and inflammation

Early untreated HIV infection is associated with sustained high-level inflammation and T-cell activation *[68-70]*. The degree of T-cell activation during untreated HIV disease is associated with risk of subsequent disease progression, independent of other factors such as plasma HIV RNA levels and the peripheral CD4 T-cell count *[71-72]*. ART results in a rapid, but often incomplete, decrease in most markers of HIV-associated immune activation *[73-77]*. Persistent T-cell activation and/or T-cell dysfunction is particularly evident among patients who delay therapy until later stage disease (CD4 count <350 cells/mm^3) *[74, 77-78]*. The degree of persistent inflammation during treatment, as represented by the levels of IL-6, may be independently associated with risk of death *[44]*. Collectively, these observations support earlier use of ART for at least two reasons. First, treatment decreases the level of inflammation and T-cell activation, which may be associated with reduced short-term risk of AIDS- and non-AIDS-related morbidity and mortality *[44, 79-80]*. Second, because the degree of residual inflammation and/or T-cell dysfunction during ART appears to be higher in patients with lower CD4 cell nadirs *[74, 77-78]*, earlier treatment may result in less

residual immunological perturbations on therapy, and hence less risk for AIDS- and non-AIDS-related complications **(CIII)**.

Prevention of HIV Transmission

Prevention of mother-to-child transmission

Effective ART reduces transmission of HIV. The most dramatic and well-established example of this effect is the use of ART in pregnant women to prevent mother-to-child transmission (MTCT) of HIV. Effective suppression of HIV replication, as reflected in plasma HIV RNA, is a key determinant in reducing perinatal transmission. In the United States, the use of combination ART during pregnancy has reduced the HIV transmission rate from approximately 20%–30% to <2% *[81]*. Thus, use of combination ARV drug regimens is recommended for all HIV-infected pregnant women to prevent MTCT of HIV **(AI)**, even if the mother does not meet the criteria for initiation of therapy for treatment of her HIV infection. Following delivery, considerations regarding continuation of the ARV regimen for maternal therapeutic indications are the same as for other nonpregnant individuals. For detailed recommendations, see ***Perinatal Guidelines*** *[82]*.

Prevention of sexual transmission

Emerging evidence supports the concept of "treatment as prevention" of sexual transmission of HIV. Lower plasma HIV RNA levels are associated with decreases in the concentration of the virus in genital secretions *[83-84]*. Studies of HIV serodiscordant heterosexual couples have demonstrated a relationship between the level of plasma viremia and HIV transmission risk: when plasma HIV RNA levels are lower, transmission events are less common *[85-89]*. These investigations, as well as other observational studies and modeling analyses demonstrating a decreased rate of HIV transmission among serodiscordant heterosexual couples following the introduction of ART, suggest that suppression of viremia in ART-adherent patients with no concomitant sexually transmitted infections (STIs) substantially reduces the risk of HIV transmission *[88-93]*. Based on these studies, the use of effective ART regardless of CD4 count is likely to reduce transmission to the uninfected sexual partner **(BII)**.

POTENTIAL LIMITATIONS OF EARLIER INITIATION OF THERAPY

Although there are benefits associated with earlier initiation of ART, there are also potential limitations to this approach. Concerns about long-term toxicity and the development of ARV resistance have served as a rationale for the deferral of HIV therapy. Earlier initiation of ART at higher CD4 counts (e.g., >500 cells/mm^3) results in greater cumulative time on therapy. Assuming treatment for many decades after initiation, the additional therapy represents a small percentage of the total time on ART for most patients.

Although newer ARV regimens are generally better tolerated, more convenient, and more potent than older regimens, there are fewer longer term safety data for the newer agents. Analyses supporting ART initiation at CD4 counts >350 cells/mm^3 (e.g., NA-ACCORD and ART-CC) were conducted with cohorts largely treated with regimens less commonly used in clinical practice. These studies reported on clinical endpoints of death and/or AIDS disease progression but lacked information on drug toxicities, resistance, or adherence. Therefore, in considering earlier initiation of therapy, concerns for some adverse consequences of ART remain.

Antiretroviral Drug Toxicities and Quality of Life

Earlier initiation of ART extends exposure to ARV agents by several years. The D:A:D study found an increased incidence of cardiovascular disease associated with cumulative exposure to some drugs within the nucleoside reverse transcriptase inhibitor (NRTI) and protease inhibitor (PI) classes *[38, 94]*. In the SMART study, continuous exposure to ART has been associated with significantly greater loss of bone density compared with interruption or deferral of therapy *[46]*. There may be unknown complications related to cumulative use of ARV drugs for many decades. A list of known ARV-associated toxicities can be found in **Adverse Effects of Antiretroviral Agents**.

Although ART frequently improves quality of life among symptomatic patients, it may also be associated with reduced quality of life in some patients, especially those who are asymptomatic at initiation of therapy. Although better tolerated and easier to administer than older drugs, most ARV drugs now used in first-line regimens can cause side effects that may reduce quality of life. Efavirenz (EFV), for example, can cause neurocognitive or psychiatric side effects, and all the PIs have been associated with gastrointestinal side effects. Furthermore, some patients may find that the inconvenience of taking medication every day outweighs the overall benefit and might choose to delay therapy whenever possible.

Drug Resistance

Very early treatment initiation may lead to an earlier onset of drug resistance selection in nonadherent patients. The consequent harm is loss of important drugs or drug classes and risk of transmission of drug-resistant HIV. Some asymptomatic patients may be less motivated to remain adherent to their HIV treatment regimens if treatment is initiated far in advance of an immediate risk of HIV-associated morbidity and mortality. The greater convenience and potency of current ARV regimens facilitate adherence and reduce the risk of ARV resistance. One study suggests that the risk of drug resistance at the time of virologic failure is lower among patients who initiated treatment at higher CD4 counts *[95]*. Treatment adherence is key to viral suppression and should be stressed prior to initiation of therapy and during follow-up visits.

Nonadherence to Antiretroviral Therapy

At any CD4 count, adherence to therapy is essential to achieve viral suppression and prevent emergence of resistance mutations. Several behavioral and social factors associated with poor adherence, such as untreated major psychiatric disorders, active substance abuse, social circumstances, patient concerns about side effects, and poor adherence to clinic visits, have been identified. Clinicians should identify areas where additional intervention is needed to improve adherence both before and after initiation of therapy. Some strategies to improve adherence are discussed in **Adherence**.

Cost

Although ART adds to the annual cost of treatment, several modeling studies support the cost effectiveness of HIV therapy initiated soon after diagnosis *[96-98]*. Studies have reported that the annual cost of care is 2½ times higher for patients with CD4 counts <50 cells/mm^3 compared with patients with CD4 counts >350 cells/mm^3 *[99]*. A large proportion of the health care expenditure in patients with advanced infection is from non-ARV drugs and hospitalization. However, no cost comparisons have been reported between those starting ART with a CD4 count between 350 and 500 cells/mm^3 versus >500 cells/ mm^3.

SUMMARY

In earlier versions of these treatment guidelines, concerns about long-term toxicity, reduced quality of life, and the potential for drug resistance served as key reasons to defer HIV therapy for as long as possible. Inherent in this argument was the assumption that the harm associated with viral replication was less than the harm associated with the toxicities of ARV drugs in patients with higher CD4 counts. There is now more evidence that untreated HIV infection has negative consequences on health at all stages of disease. Also, the drug combinations now available are better tolerated than previous regimens, leading to greater efficacy and improved adherence *[100]*. The current guidelines therefore emphasize avoiding adverse consequences of untreated HIV infection while managing potential drug toxicity.

RECOMMENDATIONS

Based on the cumulative weight of evidence described above, the Panel recommends that:

- ART should be initiated in all patients with a history of an AIDS-defining illness or with a CD4 count of <350 cells/mm^3 **(AI)**.
- ART is also recommended for patients with CD4 counts between 350 and 500 cells/mm^3 **(A/B-II)**.*
- ART should also be initiated, regardless of CD4 count, in patients with the following conditions: HIVAN **(AII)** and HBV coinfection when treatment of HBV is indicated **(AIII)**.
- A combination ARV drug regimen is also recommended for pregnant women who do not meet criteria for treatment with the goal to prevent perinatal transmission **(AI)**.
- For patients with CD4 counts >500 cells/mm^3, 50% of the Panel members favor starting ART (B); the other 50% of members view treatment as optional (C) in this setting **(B/C-III)**.
- Patients initiating ART should be willing and able to commit to lifelong treatment and should understand the benefits and risks of therapy and the importance of adherence (**AIII**).
- Patients may choose to postpone therapy, and providers, on a case-by-case basis, may elect to defer therapy based on clinical and/or psychosocial factors.

* The Panel is divided on the strength of this recommendation: 55% of Panel members voted for strong recommendation **(A)** and 45% voted for moderate recommendation **(B)**.

Conditions Favoring More Rapid Initiation of Therapy

Deferring ART may be appropriate in some cases. However, several conditions increase the urgency for therapy, including:

- Pregnancy **(AI)** (Clinicians should refer to the ***Perinatal Guidelines*** for more detailed recommendations for the management of HIV-infected pregnant women.) *[82]*
- AIDS-defining conditions **(AI)**
- Acute opportunistic infections (see discussion below)
- Lower CD4 counts (e.g., <200 cells/mm^3) **(AI)**
- Rapidly declining CD4 counts (e.g., >100 cells/mm^3 decrease per year) **(AIII)**
- Higher viral loads (e.g., >100,000 copies/mL) **(BII)**
- HIVAN **(AII)**
- HBV coinfection when treatment for HBV is indicated **(AIII)**

Acute opportunistic infections

In patients with opportunistic conditions for which there is no effective therapy (e.g., cryptosporidiosis, microsporidiosis, progressive multifocal leukoencephalopathy) but for which ART may improve outcomes by improving immune responses, the benefits of ART outweigh any increased risk, and therefore treatment should be started as soon as possible **(AIII)**.

In the setting of opportunistic infections, such as cryptococcal meningitis or non-tuberculous mycobacterial infections, for which immediate therapy may increase the risk of immune reconstitution inflammatory syndrome (IRIS), a short delay may be warranted before initiating ART *[101-102]* **(CIII)**.

In the setting of other opportunistic infections, such as *Pneumocystis jiroveci* pneumonia (PCP), early initiation of ART is associated with increased survival, and therapy should not be delayed *[3]* **(AI)**.

In patients who have active tuberculosis, initiating ART within the first 1–2 months of treatment for tuberculosis appears to confer a significant survival advantage *[103-104]*. (See ***Mycobacterium Tuberculosis* Disease with HIV Coinfection**.)

Clinicians should refer to the ***Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents*** *[105]* for more detailed discussion on when to initiate ART in the setting of a specific opportunistic infection.

Conditions Where Deferral of Therapy Might be Considered

Some patients and their clinicians may decide to defer therapy for a period of time based on clinical or personal circumstances. The degree to which these factors might argue for deferral of therapy depends on the CD4 count and viral load. Although deferring therapy for the reasons discussed below may be reasonable for patients with high CD4 counts (e.g., >500 cells/mm^3), deferral for patients with much lower CD4 counts (e.g., <200 cells/mm^3) should be considered only in rare situations and should be undertaken with close clinical follow-up. A brief delay in initiating therapy may be considered to allow a patient more time to prepare for lifelong treatment.

When there are significant barriers to adherence

Deferring treatment for patients with higher CD4 counts who are at risk of poor adherence may be prudent while the barriers to adherence are being addressed. However, increased urgency for ART (see above) may override potential predictors of poor adherence.

Several methodologies exist to help providers assess adherence. When the most feasible measure of adherence is self-report, this assessment should be completed at each clinic visit, using one of the available reliable and valid instruments *[106-107]*. If other objective measures are available (e.g., pharmacy refill data, pill count), these methods should also be implemented as therapy begins *[108-110]*. Continuous assessment and counseling make it possible for the clinician to intervene early to address barriers to adherence occurring at any point during treatment.

Presence of comorbidities that complicate or prohibit antiretroviral therapy

Deferral of ART may be considered when either the treatment or manifestations of other medical conditions could complicate the treatment of HIV infection or vice versa. Examples include:

- Patients requiring surgery that might result in an extended interruption of ART.
- Patients taking medications that have clinically significant drug interactions with ART and for whom alternative therapy is not available.

In each of these cases, it is assumed that the situation is temporary and that ART will be initiated after the conflicting condition has resolved.

There are some less common situations in which ART may not be indicated at any time while CD4 counts remain high. In particular, such situations include patients with a poor prognosis due to a concomitant medical condition who would not be expected to gain survival or quality-of-life benefits from ART. Examples include patients with incurable non-HIV-related malignancies or end-stage liver disease who are not being considered for liver transplantation. The decision to forego ART in such patients may be easier in those with higher CD4 counts; they are likely asymptomatic for HIV, and their survival is unlikely to be prolonged by ART. However, it should be noted that ART may improve outcomes, including survival, in patients with some HIV-associated malignancies (e.g., lymphoma or Kaposi's sarcoma) and in patients with liver disease due to chronic HBV or HCV.

Elite HIV controllers or long-term nonprogressors

A small subset of ARV-untreated HIV-infected persons (~3%–5%) are able to maintain normal CD4 cell counts for many years (long-term nonprogressors), while an even smaller subset (~1%) are able to maintain suppressed viral loads for years (elite controllers). It is possible that such patients would not benefit from ART. However, some nonprogressors have high viral loads, and some elite controllers progress clinically or immunologically *[111-112]*. Although therapy may be theoretically beneficial for patients in either group, clinical data supporting therapy for nonprogressors and elite controllers are lacking.

THE NEED FOR EARLY DIAGNOSIS OF HIV

Fundamental to the earlier initiation of therapy recommended in these guidelines is the assumption that patients will be diagnosed early in the course of HIV infection, making earlier initiation of therapy an option. Unfortunately, most HIV-infected patients are not diagnosed until they are at much later stages of disease *[113-116]*. Despite the 2006 Centers for Disease Control and Prevention (CDC) recommendations for routine, opt-out HIV screening in the health care setting *[117]* regardless of perceived risk of infection, the median CD4 count for newly diagnosed patients remains in the ~200 cells/mm^3 range. (The exception is pregnant women diagnosed during prenatal care, who have a much higher median initial CD4 count.) Delay in HIV diagnosis is more often seen in nonwhites, injection drug users, and older patients; a substantial proportion of these individuals develop AIDS-defining illnesses within 1 year of diagnosis *[113-116]*. Therefore, for the current treatment guidelines to have maximum impact, routine HIV screening per current CDC recommendations is essential. It is critical that all newly diagnosed patients be educated about HIV disease and linked to care for full evaluation, follow-up, and management. Once in care, focused effort is required to retain patients in the health care system.

CONCLUSION

The current recommendations are based on increasing evidence that supports earlier initiation of ART than was advocated in previous guidelines. The strength of the recommendations varies with the quality and availability of existing evidence. Panel members are divided regarding the strength of recommendations for starting therapy in patients with higher CD4 cell counts, as discussed above. The Panel will continue to monitor and assess the results of ongoing and planned randomized clinical trials and observational studies, which will provide the Panel with additional guidance to form future recommendations.

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